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PHARMACOLOGICAL AND PHYSIOLOGICAL STUDIES OF THE SWEAT CENTERS

II. ON THE EFFECT OF DIRECT MECHANICAL, THERMAL AND ELECTRICAL STIMULATION ON THE SWEAT AND HEAT CENTERS

Dr. Bun-ichi Hasama

Translation of "Pharmakologische und physiologische Studien über die Schweiss-zentren. II. Mitteilung: Über den Einfluss der direkten mechanischen, thermischen und elektrischen Reizung auf die Schweiss-sowie Wärmezentren.", Archiv. f. exp. Path. u. Pharmakol., Vol. 146, 1929, pp. 129 - 161.

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16. Abstract

A thermogenetic area was found in the subthalamic region of the cat, with both mechanical and electrical stimuli. The same zones gave a temperature rise with cold stimulus and temperature lowering with heat stimulus. Other relations were shown between heat and sweat centers. The sweat-producing impulses produced by heat are apparently carried by parasympathetic nerves, and those produced by cold are carried by sympathetic nerves.

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II. ON THE EFFECT OF DIRECT MECHANICAL, THERMAL AND ELECTRICAL STIMULATION ON THE SWEAT AND HEAT CENTERS

Dr. Bun-ichi Hasama

The mechanism of central heat regulation has repeatedly /129* been the object of detailed study, without the various authors having arrived at any uniform opinion. Most of the opinions presented in this field have not attained general acceptance. The exact anatomical determination of the heat centers is not yet complete, in spite of many attempts at it. At present, there are two different opinions with regard to the localization of the heat centers. Sachs and Aronson [1], who were able to produce temperature rises with great regularity by injury to the Corpus striatum, and especially to the caudal nucleus, localized the heat centers in the Corpus striatum. But on the other hand, Krehl, Isenschmid and Schnitzler [2, 3], on the basis of their extensive systematic experiments on removal of various parts of the brain, came to the conclusion that the parts important for heat regulation lie ventrally and medially in the central and caudal region of the midbrain and especially in the Tuber cinereum. While it was previously well known that the Corpus striatum and particularly the caudal nucleus were the location at which hyperthermia could most easily and constantly be produced by heat puncture, newer works have shown that one can likewise

* Numbers in the margin indicate pagination in the original foreign text.

produce a high temperature rise regularly by puncturing the Thalami optici. In spite of these numerous observations, we can still consider the question of where heat puncture hyperthermia is based to be unsolved. / 130

Because of the strong effect which medications introduced into the third ventricle have on the body temperature, Jacobj [4] arrived at the opinion that the parts of the brain directly adjacent to the third ventricle are particularly important for thermal regulation. On the basis of his experiments and observations, he maintained that the appearance or absence of heat puncture hyperthermia depended primarily on whether or not the wall of the third ventricle was stimulated somewhere. Isenschmid and Schnitzler [2] conjectured that that part of the forebrain sent out impulses which were not unimportant for thermal regulation, and which perhaps led to the Tuber cinereum. They also reported that, in comparison with the Tuber cinereum, all other parts of the central nervous system, and especially the forebrain, were of minor, subordinate importance for thermal regulation, because they found that an animal without forebrain, Corpus striatum, and cerebral hemispheres regulated its body temperature just as well as a normal animal, while the capability for heat regulation was destroyed on surgical removal of the Tuber cinereum. In spite of the great advances which have been made during the last decade in research on central heat regulation, many gaps still yawn in our knowledge of the effect of the central nervous system on secretion of sweat. From the latest works, one can consider it established that there is in the brain a center which controls sweat secretion. Since then, Karplus and Kreidl [5] and then also Winkler [6] have shown that there is such a sweat center in the Regio subthalamica. Electrical stimulation of this region in cats produces profuse secretion of sweat on the four paws. This raises the question of where the control of sweat secretion starts and how it functions, an important and interesting problem. The experimental results mentioned above suggest that the midbrain plays a significant role both for heat regulation and for sweat secretion. My previous experiments [12] with intracerebral injection of convulsant poisons also were able to show a notable relation of a certain point in the Regio subthalamica to heat regulation as well as to sweat secretion. So far, the main attmepts have been to discover the heat center by using the removal method, while stimulation experiments to establish the localization of the heat centers in the intact brain have not been used much. Further studies with finer mechanical stimuli of the midbrain are necessary for closer anatomic determination of the heat regulation centers and the sweat secretion centers in the midbrain. In particular, we must attempt stimulation of the Tuber cinereum and its close vicinity. All the methods which attack the basal structures through the cerebrum are unsatisfactory, because one injures the cerebral hemispheres and the Ammons horns to a more or less great extent. This is avoided with a surgical technique similar to that which Karplus and Kreidl [5] used for their stimulation experiments in this region. /131

Therefore, I have attempted to operate with the intact brain; that is, to lift the intact hemisphere laterally from the base of the skull enouch so that the midbrain is accessible from below. The present experiment primarily concerns the question of whether the direct mechanical or electrical stimulation of the Regio subthalamica with a fine needle or electrode exerts a definite influence on the body temperature and sweat secretion. In pursuing the experiment further, the effect of thermal stimulation of the Regio subthalamica on body temperature and sweat secretion was studied. The experimental results of Barbour [7] and Hashimoto [8] show that the blood temperature, with a deviation above or below the normal, is an adequate physiological stimulus for the heat centers. So far, however, the effect of caloric stimulation on the Corpus striatum has been investigated primarily and extensively with the damaged brain. Furthermore, Kahn [9] has established that the rise in the blood temperature exerts an adequate stimulus on the sweat centers. On looking through the literature to date, however, we find no attempt to affect the temperature of the sweat centers directly. In my experiment, various parts of the Regio subthalamica were directly warmed or cooled by means of a fine thermode, independent of the blood flow, so as to observe both the physiological function of the heat and sweat centers and to determine the exact location of both centers, because, to my knowledge, such stimulation experiments on the Regio subthalamica have not yet been done with intact brain.

Methodology /132

Medium-sized mature cats, normally fed, were used for the experiments. Furthermore, I selected only cats with foot pats which were soft, and not markedly cornified. In these animals, one can observe sweat secretion better on the foot pads. First, the animals were tested to determine whether they were suitable for sweating experiments at all. All the cats used for the experiments were first subjected to a preliminary experiment with pilocarpine. Occasionally one finds cats which do not react to pilocarpine with any visually perceptible secretion of sweat. I used only the cats which showed a positive pilocarpine reaction. They were kept under the most nearly possible identical outer temperature conditions during each individual experiments. The experiments were done on a total of 253 cats in the months from May to July. The room temperature during the experiment was usually 21-30°C. The body temperature was measured by inserting a thermometer about 4 cm rectally into the tied-up cat. The normal temperature of the cat differs greatly individually under different conditions. With normal feeding, the usual temperature observed on cats in the months from April to July varied between 37.4 and 38.3°C. The highest temperature was 38.9°C, and the lowest was 36.5°C. Observation of the sweat secretion was always done on the footpads of both hind legs. The amount of sweat was measured by the principle of Burnschem [10]. In order to measure the amount of sweat, the sweat was soaked up into a fragment of blotting paper weighing about 100 mg, which was wiped over the entire surface of the balls of the feet and of the toes. After the paper had soaked up the sweat, it was weighed as quickly as possible on a torsion balance so as to avoid evaporation of the sweat.

Study of the sweat secretion was done every 5 minutes. In order to exert the isolated direct stimulation on the Region subthalamica, all methods attacking the basal region through the cerebral hemispheres are unsatisfactory because they always more or less injure the cerebral hemispheres and the Ammons horns. I have avoided this by raising the intact hemisphere laterally from the base of the skull, according to Karplus and Kreidl [5], so far that the midbrain was accessible from below. The method used by Karplus and Kreidel to get to the base of the midbrain consists of opening the side of the skull in the temporal region as much as possible, removing the interfering soft parts with shears, and, after removing the Dura, carefully pulling the peak of the temporal lobe downward and outward, separating the hemisphere from the base of the skull. In this way, one gets a clear view of the base of the brain. In this way, it is possible to make the chiasma of the optic nerves, the Tuber cinereum and the Infundibulum visible and accessible. Initially, the animal was held lying on its back so that the top of the skull was downward. This operation was performed under light ether narcosis and with strict asepsis. After the manipulations of the Regio subthalamica were completed, the skin of the head was sewed up. The cat can tolerate this operation well and, as a rule, shows no visible disturbances in /133 its behavior. The animals operated on in this way usually lived for more than 10 days after the operations. Most of the cats ate with a good appetite after the operation. For the mechanical stimulation, a probe was placed vertically some 3mm into the brain substance. I made the probe with a fine needle, with simultaneous checking of the site of probing. The needle was removed immediately after insertion. The site of the puncture on the brain was always studied in connection with the experiment. Immediately after the experiment the animal was killed. The brain was taken out in toto and fixed in formalin solution. In order to find the fine puncture channel of the needle again, the needle was coated with India ink. In order to heat or cool the midbrain base directly, I used a thin-walled double metal tube according to Barbour's principle [7], through which one can pass either hot or cold water, as desired. The tip of the metal tube, with a width of about 2 mm, was placed without force at the desired region of the Regio subthalamica, for 30 minutes in most cases. One opening of the metal tube was connected to a large flask of water by means of a rubber tube, through which the water flowed. The flask with the water was placed on a tripod, somewhat higher than the head of the animal. The temperature of the water was controlled with a flame. The hot water was usually applied at a temperature of 48-52°C, measured in the upper vessel. Before the water entered the head of the animal, it usually lost 2°C, so that the heat applied in the centers was as a rule 46-50°C. Ice water was used as the cold stimulus. This usually reached the brain at 5 - 8°C. The hot or cold water, as required, was allowed to flow through the whole system at a rate of 35-40 cm^3 per minute. For electrical stimulation, I performed the stimulation at various sites with induced current, using the DuBois-Reymond step inductorium and platinum electrodes.

Experimental Results

1. The effect of direct mechanical stimulation of the various regions of the Regio subthalamica on the body temperature and the sweat secretion

The experimental results of Jacobj and Römer [4], who found a rise in temperature on injury to the wall of the third ventricle and introduction of stimulants into the third ventricle can be explained, according to them, as being due to stimulation of the nearby heat center. In particular, the fact that the introduction of mercury into the Infundibulum leads to a very strong, long-maintained hyperthermia suggests that the heat center is in the nearby wall of the Tuber cinereum. They maintained that the heat puncture hyperthermia depends primarily on the stimulus exerted on the wall of the ventricle. If this is actually a thermogenetic site, then it seems probable to me that it would react to puncture with a rise in temperature. In order to establish the truth of this hypothesis experimentally, the present experiments were done. In the cat, three parts of the Regio subthalamica can be recognized at first glance: at the front is the crossing of the optic nerves; the infundibulum with the pituitary body and the Tuber cinereum project immediately behind it; behind this is the Corpus mammillare, which is divided into two halves in this animal as in man, forming paired hemispherical projecting bodies. I performed the mechanical stimulation in the three structures mentioned, corresponding to their position. /134

a) Stimulation of the Tuber cinereum

Ott [11] has already mentioned that a stronger effect on the body temperature can be obtained at the base of the midbrain, and especially the Tuber cinereum, on stimulation than at other points in the central nervous system. Other investigations by Isenschmid and Schnitzler [2], with the object of determining the sites at which the least injury completely eliminated the heat regulation showed that the regulatory ability can be localized in the Tuber cinereum, quite possibly in the anterior portion and a region which is from one to a few millimeters away from the center line. In my own experiments [12], I was also able to demonstrate that intracerebral injection of convulsant poisons into the peri-infundibular region results in an intense lowering of the temperature, while the temperature remains almost unchanged on injection at other sites. The Tuber cinereum consists essentially of gray substance containing nerve cells. Its lumen forms the ventral sacculation of the third ventricle. After surgical separation of the base of the brain, there is usually a transient lowering of the temperature, the duration and depth of which depend on many factors, including the duration of the narcosis, the temperature of the room and of the operating table, as well as on the degree of the so-called shock. In order to avoid severe cooling of the operated animal, it was held in a heated chamber, where the temperature was 25° to 30°C for a time immediately after the operation. After the temperature had completely or almost completely returned to its original level, which was usually the case within 2 - 3 hours after the operation, the punctures were /135 made in various regions. On puncture, the animal showed slight unrest or avoidance movement.

Starting with the reports of Isenschmid and Schnitzler [2], I first made the puncture in the midline. This did not produce a significant rise in temperature. On the other hand, as expected, an intensive rise in temperature occurred after puncture in a region 1 - 3 mm away laterally from the midline. After puncture, the temperature curve usually rises rather sharply, reaching its maximum after some 2 hours. But the temperature usually decreases to the initial level within 8 hours from the beginning of the puncture. As can be seen from Table 1, 12 experiments done in the months of April and May produced an average rise of 2°C above the initial temperature. In this case, the duration of the temperature elevation is briefer than that of heat puncture hyperthermia in rabbits. Along with the puncture, pupillary dilation and contraction of the vessels in the earlobes also appeared, recalling symphatetic stimulation. These phenomena last some 3 hours and usually disappear entirely within 5 hours. Although the Tuber cinereum reacted to the mechanical stimulation with a significant rise in temperature, no sweat-producing action could be observed. These results suggest that the mechanical stimulation of the heat centers is a sufficient cause for the rise in temperature, but not an adequate stimulus for the sweat centers. I have undertaken still other experiments with the intent of establishing more accurately how far the thermogenetically active region extends laterally. Puncture of the parts which lie 4 mm laterally from the midline also causes a rise in temperature. But this is less distinct and shorter than those which occurred on stimulation at the previous site. But if one makes the puncture in a part which is 5 mm laterally from the midline, no significant change in temperature occurs any more. The protocol for the investigation is tabulated on page 10.

Now let us consider the individual experiments, using the protocol. In spite of the individual differences, we can recognize the following common points. The region of the Tuber cinereum, if it is no more than some 4 mm to the side of the midline, is a thermogenetic site. The most significant effects are produced by puncture in the portion which is no less than 1 mm and no more than 3 mm laterally from the midline. /137

Table 1. RESULTS FROM NEEDLE PUNCTURE IN VARIOUS REGIONS OF THE TUBER CINEREUM*

Point of puncture	Midline				Laterally from the midline																			
					1 mm				2 mm				3 mm				4 mm				5 mm			
Experiment No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Body weight in g.	2370	2600	2100	2570	1980	3000	2200	2350	2250	2400	1970	2100	2580	1900	1890	2470	2830	1990	2100	2130	2270	2800	1990	2130
Sex	♂	♂	♀	♂	♀	♂	♀	♀	♀	♂	♀	♂	♂	♂	♂	♀	♀	♂	♂	♂	♀	♀	♂	♀
Room temperature, °C	20 to 22	19 to 21	18 to 19	21 to 23	23 to 26	20 to 22	19 to 20	22 to 24	20 to 22	21 to 23	22 to 25	20 to 22	18 to 19	17 to 18	22 to 24	20 to 23	21 to 24	19 to 22	20 to 22	21 to 23	20 to 22	21 to 23	20 to 22	22 to 25
Rise in the body temperature, °C	0,8	1,0	0,6	1,1	1,9	2,3	2,1	1,7	2,0	1,5	1,9	2,6	2,1	2,0	1,8	1,9	0,9	1,2	0,9	0,6	0,2	—	—	0,2
Duration of the rise in hours	5	3	2	4,5	7,5	8,5	9	7	6,5	8	9	9,5	8	7	7,5	8,5	5,5	6	4	3	1	—	—	0,5

*Translator's Note: Commas in numbers represent decimal points.

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The more distant, medially or laterally, the puncture is from this region, the less effective it is.

b) Stimulation of the Infundibulum

It has been established from the observations of Krehl's school that a transverse incision in front of the infundibulum or the Tuber cinereum does not significantly affect heat regulation, and, in contrast, a transverse incision through these parts of the brain, and caudally from them, always completely eliminates heat regulation. These experiments showed that not only the Tuber cinereum, but also the infundibulum, are of decisive significance for heat regulation. The present series of experiments is directed toward the question of whether the Tuber cinereum or the infundibulum has the stronger thermogenetic action. I first made the puncture carefully on the infundibulum alone, without injuring the immediately adjacent Tuber cinereum. The results of this series of investigations are shown in Table 2 (see page 12).

If one looks at the results in the table, one is struck by the fact that a rapid strong rise in temperature takes place after the puncture. The body temperature begins to rise after only 30 minutes, reaches its maximum within 2 hours after the puncture, and then gradually returns to its original height, which was usually reached after 7 - 8 hours. Four experiments gave an average rise of 2.1°C above the initial temperature. If one compares the highest temperature rise in this case with those on puncture in the Tuber cinereum, one observes no distinct difference. Also, this process produces no rise in the sweat secretion. One observes pupillary dilation and vascular contraction in the ear lobes, however. Further investigation showed that the parts at the height

Table 2. RESULTS FROM NEEDLE PUNCTURE IN VARIOUS REGIONS OF THE INFUNDIBULUM.[*]

Site of puncture	Immediately adjacent to the infundibulum				Lateral from the infundibulum: 1 mm				2 mm				3 mm				4 mm			
Experiment Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Body weight in grams	1990	2650	2360	1980	1780	2550	2370	2600	2480	2570	2800	2670	2470	2380	2270	2500	2430	2000	2170	2230
Sex	♂	♂	♂	♀	♂	♀	♀	♂	♂	♂	♀	♀	♂	♀	♂	♂	♂	♀	♀	♂
Room Temperature in °C	20 to 23	22 to 24	23 to 25	21 to 23	20 to 23	19 to 22	18 to 21	21 to 22	18 to 21	17 to 19	19 to 21	16 to 18	20 to 23	21 to 24	22 to 24	20 to 22	18 to 19	21 to 22	22 to 24	20 to 23
Rise in the body temperature in °C	1,8	2,5	2,3	1,9	1,6	2,0	1,8	1,9	1,6	1,5	1,1	1,0	0,9	0,7	0,5	0,8	—	0,2	0,3	—
Duration of the rise, in hours	8	8,5	9,5	7,5	7,5	8,5	7,5	8	6,5	6	5	5,5	2	2	3	2,5	—	0,5	1,5	—

*Translator's Note: Commas in numbers represent decimal points.

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of the infundibulum, as long as they were no more than 3 mm laterally from it, reacted to the puncture with a temperature rise, and the thermogenetic action is weaker, the more distant the puncture is from the infundibulum.

c) Stimulation of the Corpus mammillare

As mentioned previously, Isenschmid and Schnitzler [2] have confirmed that transverse incision caudally from the Tuber cinereum results in complete elimination of heat regulation. On the basis of this observation, they assumed that there is no part of the central nervous system caudal to the Tuber cinereum which can alone exert heat regulation in demonstrable strength without the cooperation of the Tuber cinereum. In my earlier works, however, I have referred to the fact that introduction of convulsant poisons into the Corpus mammillare, as well as injection into the Tuber cinereum, results in an intense reduction in temperature. In order to clarify whether the Corpus mammillare is also a thermogenetically active site, I also made a puncture here. At first, the punctures were made in the midline itself, but without there being any significant temperature rise. But as Table 3 shows, I was in fact able to cause a moderate rise in temperature by puncture of the regions lying from 1 to 3 mm laterally from the midline. In all of these cases, the temperature rise started after only 30 minutes and reached its maximum after 1-2 hours. The maximum, on the average, was 1.2°C above the initial temperature. Then the temperature returned gradually to its initial level. In this experimental series, however, the intensity and duration of the temperature rise were less, in comparison with those from puncture in the Tuber cinereum or the infundibulum. Also, no distinct change of the pupils and the vessels of the earlobes could be detected in this series of experiments. / 140

Table 3. RESULTS FROM NEEDLE PUNCTURE IN VARIOUS REGIONS OF THE CORPUS MAMMILLARE*

Site of puncture	Midline				Lateral from the midline																			
					1 mm				2 mm				3 mm				4 mm				5 mm			
Experiment Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	[illegible]4
Body weight in grams	1900	2210	2000	1890	1970	2400	2530	2270	2350	2290	2530	2200	2000	1970	1890	2200	2100	1900	2480	2500	2380	2290	1980	2[illegible]00
Sex	♂	♀	♂	♂	♀	♂	♀	♂	♂	♀	♂	♂	♂	♀	♂	♀	♀	♂	♂	♀	♂	♀	♂	
Room Temperature in °C	23 to 25	22 to 25	20 to 22	22 to 25	23 to 24	22 to 25	20 to 22	21 to 23	22 to 25	23 to 25	23 to 26	22 to 25	22 to 25	23 to 24	24 to 27	25 to 27	24 to 27	22 to 25	23 to 26	22 to 25	23 to 26	22 to 25	21 to 23	2[illegible] to 2[illegible]
Rise in the Body Temperature in °C	0,5	0,8	0,3	0,6	1,5	1,7	0,9	0,8	1,1	1,3	1,7	1,2	1,5	1,0	0,9	0,8	0,3	0,4	0,1	0,5	—	—	0,2	0[illegible]
Duration of the rise in hours	1,5	2,5	2	1,5	4,5	5,5	3	4	4,5	5	5,5	3,5	4	4	5,5	3,5	2	2	0,5	1,0	—	—	0,5	0,5

*Translator's Note: Commas in numbers represent decimal points.

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In addition, it could be observed that the puncture always produced a temperature rise if it was in a part which was no more than 4 mm laterally from the midline. The intensity, however, is strongest on puncture in regions lying 1 - 3 mm laterally from the midline. The farther the puncture is from this region, medially or laterally, the less the result is. Therefore, one is justified in assuming that the Corpus mammillare is also a thermogenetically active site, and thus has a certain influence on heat regulation, but with less strength than the Tuber cinereum or the infundibulum.

d) Stimulation of the regions caudal from the Corpus mammillare.

My earlier experiments have already shown that no significant temperature change is produced by intracerebral injection of convulsant poisons into this region. Isenschmid and Schnitzler were likewise of the opinion that none of the important heat regulation centers are in the midbrain /141
(mesencephalon), because a complete section through the central and rear parts of the midbrain (diencephalon) completely eliminates heat regulation. The rear edge of the Corpus mammillare corresponds to the boundary between the diencephalon and the mesencephalon. In this series of experiments, the puncture was done in a manner similar to that in the experiments previously described, in the various parts between the caudal edge of the Corpus mammillare and the frontal edge of the Pons. In no case was there a significant change in the body temperature. This is true both for puncture in the parts which are strictly medial as well as for the more lateral parts. This finding which I have established suggests, then, that the foremost portion of the mesencephalon is not a thermogenetically effective site, so that it can exert no influence on the heat balance.

c) Stimulation of regions lying frontally from the infundibulum

Isenschmid and Krehl [3] have already demonstrated that destruction of the foremost portion of the diencephalon does not result in any injury to heat regulation. Furthermore, Isenschmid and Schnitzler have established that the part of the diencephalon which is above the crossing of the optic nerves is unnecessary for heat regulation if it is frontal from the rear edge of the Chiasma. My earlier experiments [12] have shown that injection of convulsant poisons into the parts frontal from the infundibulum results in no variation in temperature. I have again attempted to determine exactly how far the thermogenetically active region extends frontally. For a better view into the base of the brain in this series of experiments, the optic nerves were cut through and removed. The experiments showed that no significant temperature variation is produced by puncture in the regions frontal from the infundibulum, whether the punctures are made strictly medially or laterally.

2. The Effect of Direct Heating or Cooling of the Regio subthalamica on Sweat Secretion and Body Temperature

Many stimuli proceeding from the Regio subthalamica are expressed in an effect on sympathetically innervated functions such as pupil dilation, vasoconstriction, sweat secretion, temperature rise and glycogen degradation. This situation indicates that, as well as the heat centers, the stimulatory centers for sweat secretion, vascular contraction, smooth musculature, and metabolic processes also lie in the Regio subthalamica. But at present we are at the very earliest beginnings with respect to knowing the exact localization of the individual functions. Even the question of which systems are to be included with those in the diencephalon is still unanswered. As is well known, the organism protects itself

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from heat by increasing heat loss, through dilating the blood vessels and by evaporation of the abundantly secreted sweat. The body protects itself from cooling by limiting heat loss, through constriction of the skin blood vessels and through reduction in perspiration, and then through increased heat production. On the basis of these facts it is obvious that heat regulation is controlled through centers which are in turn under the influence of the sweat or vasomotor centers. On the pharmacological side it has been stated, especially by H. H. Meyer [13], that the thermoregulatory equipment of the homeothermic animals consists of two central systems with different capabilities for action, a cooling and a warming center. The former is a heat-releasing center with the capability for stimulating vasodilation of the skin, the sweat glands, and the breathing rate. The latter is a heat-producing center with the ability to stimulate metabolic processes, muscular movement, and the vasoconstriction of the skin. We do not know whether they are morphologically separable, but they are probably functionally separable, to the extent that they behave antagonistically and balance, i. e., control and limit each other. Meyer has also stated that every temperature fluctuation naturally acts in the opposing sense on the antagonistic centers. Warming calms the warming center and stimulates the cooling center, while cooling acts inversely. Kahn [9] has already found that warming of the blood flowing through the Carotis to the brain produces vasodilation of the skin, sweat secretion, and heat dyspnea, all of which are symptoms of physical reaction to overheating. Introduction of cool blood, by comparison, leads to a rise of oxidation in the muscles and internal organs. That is, it initiates chemical heat production. Barbour [7] and Hashimoto [8] provided more proof by introducing into the brain fine tubes through which they could pass water at various temperatures. In this way, they could raise the body temperature with cold water and lower it with warm water. From these experimental results, one can assume that the blood temperature, with an upward or downward deviation from the normal, is an adequate physiological stimulus for the heat or sweat centers. / 143

On the basis of earlier experiments by Karplus and Kreidl [5], the base of the diencephalon is considered to be the central site of stimulation for sweat secretion. As yet, however, it has not been possible to localize the sweat centers accurately. As for the physiological function of the sweat centers, this has received little consideration. It could be unusually important for further basic research on the sweat centers to investigate systematically the physiological importance of the sweat centers for thermal regulation. Although the stimulus exerted by the blood temperature is considered to be an adequate cause for sweating, to my knowledge no experiment has yet been done in which isolated warming or cooling of the Regio subthalamica, independently of the blood stream, has been undertaken. In this experiment, therefore, I have set for myself the objective of investigating whether the direct thermal stimulation of the Regio subthalamica produces secretion of sweat. In my series of experiments, I studied the effect of caloric stimulation on the diencephalon alone, and eliminated its effect on other parts of the brain. After the cat had recovered from the surgical shock and the temperature had returned to its initial level, the thermode tip was carefully applied to the Tuber cinereum for 30 minutes. When hot water was passed through it, slight unrest and frequency of respiration was often observed in the cats.

In agreements with the report by Hashimoto, warming (48-52°C) of the Tuber cinereum resulted in lowering the temperature. Otherwise, as expected, one observed significant sweat secretion on the foot pads on the same and on the opposite side. The sweating begins after the warming, reaches its maximum within 5 - 10 minutes, and lasts for another 5 - 10 minutes after warming is stopped. Simultaneously with the sweat secretion, the temperature curve usually descends rather slowly, reaching its lowest point 20-30 minutes after the warming. After warming stops, the temperature gradually returns to its initial level, usually within 30 minutes. The warming was done five times in succession at the same site and always caused abundant sweating. The amount of sweat and the decrease in temperature were almost equally great in each case. This behavior undoubtedly indicates that, in agreement with my earlier reports, there is a central site for sweat / 144 secretion or heat regulation in the Tuber cinereum, and that it reacts to warming with significant sweat secretion as well as with a lowering of temperature. In the following series of experiments I attempted to clarify whether the Tuber cinereum alone is the center for stimulating sweat secretion and the body temperature, or whether the whole base of the diencephalon is related to sweat secretion and the body temperature. For this purpose, I warmed different sites in the Regio subthalamica at intervals of 1 hour in order to detect which basal sites produced the most abundant sweat secretion and the greatest decrease in temperature on warming. The result of one typical example is shown in Table 4 (see page 20) for a better overview.

If one looks at these, it is striking that there is a zone in the Regio subthalamica which reacts to warming with sweat secretion and temperature reduction, and which extends from the caudal end of the Corpus mammillare to the frontal edge of the infundibulum. But the region producing the greatest effect is 1 - 3 mm lateral from the midline. The farther I went laterally from this region toward the base of the temporal lobe, the less the sweat secretion and temperature decrease became. Finally, I was able to find a point at the base of the brain, beyond which neither one nor the other could be produced. This

Table 4. EXPERIMENT WITH DIRECT WARMING OF VARIOUS REGIONS OF THE REGIO SUBTHALAMICA*
Male cat, weight 2,710 g; room temperature, 20-22°C.

Site of warming	Before warming	During warming: 5 minutes	10	15	20	25	30	After warming: 35 minutes	40	45	50	55	60	Temperature reduction. Total amount of sweat
Tuber cinereum														
Body temperature in °C	37,5	37,4	37,1	37,0	36,8	36,7	36,5	36,3	36,4	36,7	37,1	37,2	37,4	1,2
Amount of sweat, mg. right		5	6	7	8	7	7	2	—	—	—	—	—	42
Amount of sweat, mg. left		4	7	7	7	8	7	2	—	—	—	—	—	42
Infundibulum														
Body temperature in °C	37,5	37,3	37,1	36,7	36,6	36,5	36,4	36,4	36,6	36,6	36,9	37,2	37,3	1,1
Amount of sweat, mg right		5	7	8	6	6	7	2	—	—	—	—	—	41
Amount of sweat, mg left		4	7	8	6	6	6	2	—	—	—	—	—	39
Corpus mammillare														
Body temperature in °C	37,6	37,6	37,5	37,3	37,1	37,1	37,0	37,0	37,2	37,4	37,5	37,5	37,5	0,6
Amount of sweat, mg right		3	5	4	5	5	4	2	—	—	—	—	—	28
Amount of sweat, mg left		2	6	5	5	4	5	3	—	—	—	—	—	30
Caudal from the Corpus mammillare														
Body temperature in °C	37,6	37,6	37,5	37,6	37,7	37,6	37,6	37,7	37,5	37,6	37,7	37,7	37,6	—
Amount of sweat, mg right		—	—	—	—	—	—	—	—	—	—	—	—	—
Amount of sweat, mg left		—	—	—	—	—	—	—	—	—	—	—	—	—
Frontal from the Infundibulum														
Body temperature in °C	37,7	37,8	37,7	37,7	37,6	37,6	37,7	37,7	37,6	37,5	37,6	37,7	37,7	—
Amount of sweat, mg right		3	5	5	4	5	5	2	—	—	—	—	—	29
Amount of sweat, mg left		4	5	5	4	4	4	2	—	—	—	—	—	28

The individual warmings (50°C) were done at 1-hour intervals, 1 mm to the right of the midline.

*Translator's Note: Commas in numbers represent decimal points.

sweat-producing or temperature-reducing zone extends some 4 mm laterally from the midline. It is worth noting that the sweat secretion and temperature reduction initiated from the Tuber cinereum and the infundibulum is greater than that caused by warming the other parts of the Regio subthalamica. The same results were always obtained, whatever the sequence of warming. The limit for the warming of the Regio subthalamica, up to which temperature reduction and sweat secretion were produced, is about 42°C. This behavior no doubt indicates that the heat stimulus on the sweat center, as on the heat center (if I may be allowed to use this expression for brevity) should be considered as an adequate physiological stimulus. I also investigated further to determine whether cold is in itself an active stimulus for increasing the temperature or for sweat secretion. Under the influence of cold on the Tuber cinereum, the temperature rose, sweat secretion occurred, and both pupillary dilation and vasoconstriction in the earlobes appeared. /146
If cold water (1 - 2 °C) was allowed to flow through the tube, then during the next 20-30 minutes the temperature rose by an average of 1.5°C. An eruption of sweat also appeared promptly as a result of the cooling, both on the footpads of the same side and on the opposite side. The cooling was repeated five times at the same site with almost identical results. The limit for cooling of the Regio subthalamica, up to which a rise in temperature was produced, is approximately 25°C. The limit, up to which sweat secretion occurred, is about 8°C.
If one compares the amount of sweat which appears with the action of cold with that from the action of heat, one finds that the former is far less than the latter (see Table 5). In further experiments which I undertook to clarify the question of which / 147
site on the base of the diencephalon produces the most abundant sweat secretion and the greatest temperature rise on cooling, I found that cooling of the region extending from the caudal margin of the Corpus mammillare to the frontal end of the infundibulum always produces a temperature rise and sweat

Table 5. EXPERIMENT WITH DIRECT HEATING OR COOLING OF THE TUBER CINEREUM*
(1 mm to the right of the midline). Male cat, 2,630 g weight;
room temperature 19°C.

Type of Stimulation	Before Stimulation	During Stimulation (minutes) 5	10	15	20	25	30	After Stimulation (minutes) 35	40	45	50	55	60	Temperature change; Total amount of sweat
Heat Stimulation (50°C)														
Body temperature in °C	37,8	37,7	37,4	37,1	36,9	36,5	36,3	36,2	36,2	36,6	36,9	37,0	37,4	−1,6
Amount of sweat, mg: right		5	6	8	7	9	8	3	—	—	—	—	—	46
Amount of sweat, mg: left		4	5	7	9	8	8	2	—	—	—	—	—	43
Cold stimulation (3 °C)														
Body temperature in °C	37,7	37,9	38,0	38,1	38,4	38,5	38,7	38,7	38,5	38,4	38,2	38,2	38,0	+1,0
Amount of sweat, mg: right		1	2	3	2	2	2	1	—	—	—	—	—	13
Amount of sweat, mg: left		1	3	2	2	3	3	1	—	—	—	—	—	15

The individual stimulations were done at intervals of 1 hour.

*Translator's Note: Commas in numbers represent decimal points.

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secretion.

Cooling of the Tuber cinereum and of the infundibulum produces sweat secretion and temperature rise of the same strength, but these are significantly stronger than those which occur on stimulation of the Corpus mammillare or of the region frontal from the infundibulum. Cooling of the region caudal from the Corpus mammillare could produce neither sweat secretion nor temperature rise. The finding which I have established indicates that cold acting on the heat centers of the Regio subthalamica produces fever, and the application of heat reduces the temperature. This makes it clear that the conditions which Barbour and Hashimoto established for the Corpus striatum apply to the heat centers in the Regio subthalamica. It has also been shown that not only warmth but also cold exerts an adequate physiological stimulus on the sweat centers.

3. The Effect of Direct Heating or Cooling of the Frontal Lobe on Sweat Secretion and Body Temperature

The question of whether there are still more sweat centers in the cerebral cortex is still unanswered, and largely unattacked. The work of Gribojedov [14], done under the direction of Bechterev, has shown that sweat secretion on the footpads can be generated in the cat from the anterior part of the Gyrus antecruciatus, and that after it is removed, secretion on heating and on movement is weaker on the opposite side than on the same side. On the basis of further observations by Winkler [6], it is established that the sweat secretion initiated from there is inconstant and insignificant. Winkler has also reported that in the cat there is a site in the medial part of the base of the frontal lobe from which sweat secretion can be initiated more constantly and abundantly than from other parts of the cerebral cortex. As previously mentioned, attempts at accurate localization of the other sweat centers in the cerebral cortex were unsuccessful for a long time. So far, it is the effect of electrical stimulation on the sweat centers which has been studied primarily and more extensively. To my knowledge, the influence of physiological thermal stimulation on the sweat centers in the cerebral cortex has not yet been investigated, in spite of its importance and significance. Proceeding on the basis of Bechterev's view, I first studied the effect of caloric stimulation of the motor region on sweat secretion. The brain was exposed and the path to the base of the frontal lobe was opened up by removal of the upper orbital wall. The operated animal was held in a warm box at 30°C until the temperature drop caused by the operation had returned to its original level. When the animal was taken out of the warm box, the foot pads were quite dry. On thermal stimulation of the exposed Gyrus antecruciatus with a thermode, I could sometimes produce slight and inconstant sweating, but a considerably higher temperature (above 50°C) was necessary. The sweating was simultaneously accompanied by epileptiform convulsions. I could produce the same result not only from the Gyrus antecruciatus, but also from the entire motor region. Continued probing of the surface of the entire cerebral cortex with the thermode showed that there is also a region in the basal field of the frontal lobe which is related to sweat secretion, while no other location produced sweat secretion. /148

On careful probing of the exposed base of the fontal lobe, it was established that a lower temperature than in the previous case produces more abundant and constant sweat secretion. On sytematic warming of the base of the frontal lobe it was established that the point of the frontal lobe from which the most abundant sweat secretion is initiated at the lowest temperature is to the front of the Chiasma. The region of the base of the frontal lobe lying immediately in front of the infundibulum, i. e., the suprachiasmatic region, was warmed for the first time. For better vision over this region, the Tractus opticus was cut through and removed. In all cases, very strong sweating occurred equally and simultaneously on both hind footpads in connection with the warming. It reached its maximum after 10 minutes. The sweating appeared promptly and lasted for several minutes after the warming was stopped. The warming was done five times in succession and was always accompanied by the same result. I have also attempted to /149 determine whether a certain point of the basal cortical field of the frontal lobe can be located as the center for stimulation of sweat secretion, or whether the entire base of the frontal lobe is related to sweat secretion. The farther I went laterally from the midline toward the sides of the cortex, and frontally from the Chiasma, the more inconstant and insignificant the experimental results became. Finally I was able to find a point on the base of the brain beyond which no sweat secretion could be stimulated. The sweat-producing zone extends some 4 mm laterally from the midline and some 4 mm frontally from the Chiasma. These results almost coincide with Winkler's reports. In contrast to the strong effect on the sweat secretion, no point on the base of the frontal lobe caused temperature variation, pupillary change, or change in the vessels of the earlobes. For clarification of these results, I refer to Tables 6 and 7.

On the basis of these experiments, it was obvious to /150 assume that the central site of stimulation for sweat secretion is not localized in the Regio subthalamica alone, but also extends toward the medial and basal region of the frontal lobe.

It was also shown that the sweat-producing zone has no distinct relation to heat regulation, although an intimate relation of the Regio subthalamica to heat regulation was established. There arose the further question of whether cold is also an active stimulant for sweat secretion. The experiments

Table 6. EXPERIMENT WITH DIRECT HEATING OF THE BASE OF THE FRONTAL LOBE. Male cat, weight 2,720 g. Room temperature 20-22°C.

Site of Heating	Midline	2 mm lateral from the midline	4 mm lateral from the midline	6 mm lateral from the midline
Amount of sweat in mg				
Right	30	25	12	3
Left	29	23	14	—

The thermode was moved from medial to lateral at a point directly in front of the Chiasma opticum. The individual heatings (50°C) were done at intervals of one hour and thirty minutes.

Table 7. EXPERIMENT WITH DIRECT HEATING OF THE BASE OF THE FRONTAL LOBE. Male cat, weight 1,970 g. Room temperature 20-22°C.

Site of Heating	Immediately behind the Chiasma	Above the Chiasma	Immediately frontal from the Chiasma	2 mm frontal from the Chiasma	4 mm frontal from the Chiasma	6 mm frontal from the Chiasma
Amount of sweat in mg						
Right	31	31	32	20	13	—
Left	32	30	30	22	15	2

The thermode was moved from caudal to frontal at the midline. The individual heatings (50°C) were done at intervals of one hour and thirty minutes.

which I undertook to answer this question show that the same zone which is affected by warming also reacts with sweat secretion under the influence of cold. This agrees with the experimental results on cooling of the Regio subthalamica. With respect to the amount of sweat produced, it is strikingly less than that which was observed on heating. The body temperature also remained unaffected on cooling.

4. Effect of Atropine and Ergotoxin on the Sweat Secretion Caused by Cold or Heat Stimulus

In spite of many attempts, the question of the innervation of the sweat glands is not yet entirely explained because parasympathetic (pilocarpine, etc.) sweating through non-demonstrable parasympathetic sweat pathways appears to be diametrically opposed to the positive result of sympathetic stimulation experiments. On the basis of my previous experiments I have reason to accept two different stimulants, heat stimulus and cold stimulus. With the former, there is abundant sweating with reduction in the temperature; and, with the latter, slight sweating with a rise in temperature.
The phenomena caused by the cold stimulus recall the phenomena on stimulation of the sympathetic heat centers. The phenomena resulting from heat stimulus recall the phenomena on stimulation of the parasympathetic cooling centers. The important recognition that the character of the sweat secretion is not identical with cold stimulus and heat stimulus was also confirmed through various clinical experiences. From experience, one can also distinguish two types of sweating, namely cold sweat and hot sweat. This fact stimulated me to the conjecture that the cold sweat is related to the sympathetic heat centers and, conversely, the hot sweating is related closely to the cooling centers. As sweat secretion, like saliva secretion, / 152
can be stimulated both by sympathetic — under special

Table 8. EXPERIMENT WITH DIRECT HEATING (50°C) OF THE TUBER CINEREUM AFTER SUBCUTANEOUS INJECTION OF ATROPINE AND ERGOTOXIN, RESPECTIVELY.* Male cat, weight 2,150 g. Room Temperature 20°C.

Types of poisoning	Before heating	During Heating						After Heating						Temperature change. Total amount of sweat.
		5	10	15	20	25	30	35	40	45	50	55	60	
		minutes						minutes						
After ergotoxin injection (3 mg per kilogram)														
Body temperature in °C	37,5	37,5	37,3	37,0	36,8	36,5	36,2	36,2	36,5	36,7	37,0	37,2	37,3	−1,3
Amount of sweat in mg, right		3	4	5	6	6	6	2	—	—	—	—	—	32
Amount of sweat in mg, left		2	5	6	7	6	7	2	—	—	—	—	—	35
After atropine injection (4 mg per kilogram)														
Body temperature in °C	37,4	37,4	37,3	37,3	37,2	37,2	37,1	37,2	37,2	37,3	37,4	37,4	37,4	−0,3
Amount of sweat in mg, right		—	2	—	2	—	—	—	—	—	—	—	—	4
Amount of sweat in mg, left		—	1	2	1	—	—	—	—	—	—	—	—	4

*Translator's Note: Commas in numbers represent decimal points.

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Table 9. EXPERIMENT WITH DIRECT COOLING (3°C) OF THE TUBER CINEREUM AFTER SUBCUTANEOUS INJECTION OF ATROPINE AND ERGOTOXIN, RESPECTIVELY.*
Female cat, weight 2,000 g. Room temperature 21°C.

Types of poisoning	Before cooling	During Cooling (minutes) 5	10	15	20	25	30	After cooling (minutes) 35	40	45	50	55	60	Temperature change. Total amount of sweat.
After atropine injection (4 mg per kilogram)														
Body temperature in °C	37.2	37.3	37.5	37.7	37.8	38.0	38.1	38.2	38.4	38,4	38.2	38.0	37.6	+1.2
Amount of sweat in mg. right		1	2	2	3	2	1	1	—	—	—	—	—	12
Amount of sweat in mg. left		1	2	2	2	2	1	1	—	—	—	—	—	11
After ergotoxin injection (3 mg per kilogram)														
Body temperature in °C	37.4	37,4	37,5	37,4	37,4	37,5	37,4	37,4	37,5	37,5	37,4	37,4	37,4	—
Amount of sweat in mg. right		—	—	—	—	—	—	—	—	—	—	—	—	—
Amount of sweat in mg. left		—	—	—	—	—	—	—	—	—	—	—	—	—

*Translator's Note: Commas in numbers represent decimal points.

conditions — and by parasympathetic ending poisons, it is not improbable that the sweat glands, for which only sympathetic fibers have been demonstrated anatomically so far, are, like other autonomous organs, doubly innervated. Admittedly, this idea is still hypothetical at present. But it is of great importance from the pharmacological standpoint to clarify whether the sweat-generating impulses due to stimulation of the sweat centers are conducted to the active organs through the parasympathetic pathways. For this reason, I concerned myself first with the influence of ergotoxin and atropine on sweat secretion due to the action of cold. After the subcutaneous injection of ergotoxin at 3 mg per kilogram had produced complete sympathetic paralysis, the Tuber cinereum was cooled for 30 minutes with a thermode. While the minor sweat secretion and temperature rise caused by cold stimulus were eliminated by ergotoxin, both of them remained almost unaltered with atropine injection. In contrast to this, the abundant sweating and temperature reduction produced by the action of heat was prevented by pretreatment with 4 mg atropine per kilogram, but not by ergotoxin.

This fact gives rise to the conjecture that the sweat glands are doubly innervated by two different nerves, parasympathetic and sympathetic (see Tables 8 and 9, page 28).

The occurrence of the two different types of sweat secretion depend on whether or not the sympathetic or the parasympathetic system is stimulated.

5. Influence of Electrical Stimulation of the Regio subthalamica and the Base of the Frontal Lobe on Body Temperature and Sweat Secretion

In this investigation, I stimulated various sites with induced current, using the step inductorium and the platinum electrode. Probing the Tuber cinereum with the electrode pair also produced abundant sweat secretion, temperature rise, pupillary dilation and vasoconstriction as a rule. The zone which acts to produce sweat and raise the temperature on electrical stimulation is, as already ascertained, not only in the Tuber cinereum, but also extends from the caudal margin of the Corpus mammillare to the frontal margin of the infundibulum. It extends 4 mm laterally from the midline. At the level of the Tuber cinereum, and of the Corpus mammillare, the zone /154 which produces the strongest eruption of sweat and the most significant temperature rise is 1 - 3 mm lateral from the midline. With stimulation nearer to or farther from the midline than this region, the less significant is the result. At the height of the infundibulum, however, the sites nearest to it react with the most intensive sweating and the strongest rise in temperature.

Further sampling of the frontal lobe confirmed that the site of stimulation for sweat secretion is extended toward the medial and basal regions. The further laterally from the midline and frontally from the Chiasma the stimulation is done, the less, and less regular, the sweating becomes. Finally, I could find one place which did not react with any sweat secretion to probing with the electrode pair (see Table 10, page 32).

This zone which reacts to electrical stimulation by secreting sweat corresponds to that found in the experiments with caloric stimulation. In contrast to the significant effect on sweat secretion, no temperature change was caused at the

Table 10. EXPERIMENT WITH DIRECT ELECTRICAL STIMULATION OF THE DIFFERENT AREAS OF THE REGIO SUBTHALAMICA.*
Male Cat, weighing 2,370 g. Room temperature 19-21°C.

Site of the stimulation	Before Stimulation	During Stimulation						After Stimulation						Temperature rise. Total amount of sweat
		5	10	15	20	25	30	35	40	45	50	55	60	
		minutes						minutes						
Tuber cinereum														
Body temperature in °C	37,8	37,9	38,3	38,7	39,0	39,1	39,3	39,3	39,1	38,8	38,5	38,2	38,0	1,5
Amount of sweat in mg, right		3	6	7	7	6	8	2	—	—	—	—	—	39
Amount of sweat in mg, left		2	7	6	8	6	7	2	—	—	—	—	—	38
Infundibulum														
Body temperature in °C	37,9	37,9	38,1	38,5	38,8	39,0	39,1	39,2	39,1	38,7	38,6	38,3	38,1	1,3
Amount of sweat, mg, right		2	5	6	7	6	8	3	—	—	—	—	—	37
Amount of sweat, mg, left		2	6	7	8	7	6	2	—	—	—	—	—	38
Corpus mammillare														
Body temperature in °C	37,7	37,7	37,9	38,0	38,2	38,3	38,4	38,4	38,4	38,2	38,1	38,0	37,9	0,7
Amount of sweat, mg, right		2	4	4	5	6	5	2	—	—	—	—	—	25
Amount of sweat, mg, left		2	3	5	5	4	6	3	—	—	—	—	—	28
Caudal from the Corpus mammillare														
Body temperature in °C	37,8	37,8	37,8	37,8	37,9	37,8	37,7	37,9	37,8	37,7	37,8	37,7	37,8	—
Amount of sweat, mg, right		—	—	—	—	—	—	—	—	—	—	—	—	—
Amount of sweat, mg, left		—	—	—	—	—	—	—	—	—	—	—	—	—
Frontal from the infundibulum														
Body temperature in °C	37,8	37,8	37,7	37,8	37,9	37,8	37,8	37,7	37,8	37,8	37,8	37,8	37,7	—
Amount of sweat, mg, right		2	5	4	4	5	5	2	—	—	—	—	—	27
Amount of sweat, mg, left		3	5	5	5	4	6	2	—	—	—	—	—	30

Stimulation was done at 1-hour intervals 1 mm to the right side of the midline. Battery current 5 V, coil separation 8 cm.

*Translator's Note: Commas in numbers represent decimal points.

basal field of the frontal lobe. If one paints the Regio subthalamica and the basal cortical field of the frontal lobe with 10% cocaine solution, neither electrical nor caloric stimulation have any effect on sweating, temperature rise, and other sympathetic stimulation phenomena. Stimulation of the motor region, especially of the Gyrus antecruciatus, likewise produces sweating which is accompanied by epileptiform convulsions. But it is slight and inconstant, and a considerably stronger current is needed to initiate sweating than on stimulation of the base of the frontal lobe. Thus, this is probably the minor sweating which is well known as a phenomenon accompanying convulsions.

6. Effect of a Shift in Hydrogen Ion Concentration in the Sweat Centers on Sweat Secretion

The well known fact that sweating is accompanied by accelerated breathing leads us to the conjecture that the sweat centers are also stimulated by increased carbonic acid content in the blood; that is, by the shift of the blood hydrogen ion concentration toward the acid side. If this is really an effect of the change in the hydrogen ion concentration of the blood on the sweating centers, then it must be possible to initiate sweating independently of the blood stream by direct application of acidic solution in the Regio subthalamica. /155
For this experiment, I used Ringer solution, made strongly acidic or alkaline by addition of hydrochloric acid or sodium bicarbonate. First, the region of the Tuber cinereum was swabbed with acidified ringer solution (pH 3), but there was no effect on sweating and on the body temperature. Direct application of the solution in the brain substance of the Tuber cinereum, in contrast, led to sweating and a temperature rise. The needle point was first inserted into the brain substance. The fine needle tip, wrapped with absorbent cotton, was then immersed in the acidic solution (pH 3) and placed in the

Table 11. EXPERIMENT WITH DIRECT APPLICATION OF ACIDIC RINGER SOLUTION (pH 3) INTO THE TUBER CINEREUM (1 mm to the right side of the midline).*
Male cat, weight 1,930 g. Room temperature, 19-22°C.

	Before the Application	After the Application																				Temperature Rise. Total amount of sweat.
		5	10	15	20	25	30	35	40	45	50	55	1	2	3	4	5	6	7	8	9	
		minutes											hours									
Body temperature in °C	37.3	37.4	37.4	37.6	37.9	38,0	38,3	38,5	38,6	38,9	39,0	39,3	39,5	39,3	39.4	38.7	38,3	38.0	37.9	37.5	37.5	2.2
Amount of sweat in mg right		3	5	6	8	8	7	5	2	—	—	—	—	—	—	—	—	—	—	—	—	44
left		4	5	6	7	8	8	6	3	2	—	—	—	—	—	—	—	—	—	—	—	49

*Translator's Note: Commas in numbers represent decimal points.

puncture in the Tuber cinereum, where it was left for 2 -3 minutes.

On application, there was prompt secretion of sweat evenly on both foot pads. The secretion reached its maximum within 10 minutes and lasted 30 minutes. With respect to the change in temperature, a significant rise could also be established. It was usually more intense and lasting than that from simple puncture. The same phenomenon was always produced from the entire region of the sweat-generating zone. In contrast, the strongly alkaline solution (pH 10) had practically no effect on sweating or body temperature. Table 11 (page 34) shows by means of a typical example the result of direct application of the acidic Ringer solution into the Tuber cinereum. / 156

Discussion of the Results

Through a series of the previous experiments, I was able to localize a certain part of the Regio subthalamica which reacts thermogenetically to mechanical and electrical stimulation. This heat-producing zone extends from the caudal margin of the Corpus mammillare to the frontal margin of the infundibulum. From that zone, I could produce the longest-lasting and most significant temperature rise from the Tuber cinereum. Along with the rise in temperature, one can also observe pupillary dilation and contraction of the vessels in the earlobes, suggesting sympathetic stimulation. This zone corresponds to the essential region for heat regulation of Krehl's school. In spite of the many investigations, so far the question of where heat puncture hyperthermia is based is still unsolved. While the Corpus striatum and especially the caudal nucleus were, as is well known, considered to be the point from which the heat puncture hyperthermia could most easily and constantly be produced, on

the basis of my experiments the heat puncture hyperthermia can also be produced from the Regio subthalamica and especially, most strongly and constantly, from the Tuber cinereum. To generate heat puncture hyperthermia it is, then, unconditionally necessary to puncture the Corpus striatum. This situation argues for the assumption of Jacobj and Römer, that the very intense and enduring hyperthermia produced by placing irritating substances such as mercury into the infundibulum is due to stimulation of the heat centers in the adjacent wall of the Tuber cinereum. The stimuli proceeding from the Regio subthalamica are also expressed in an effect on sympathetically innervated functions such as pupillary dilation and vasoconstriction in the earlobes. From this, one must conclude that there is also a center for sympathetically innervated functions in the Regio subthalamica. As the sympathetic system participates extensively in heat regulation, one is justified in assuming that the significance of the Tuber cinereum for heat regulation is subordinate to that of the Corpus striatum. It is also obvious to conjecture that the so-called heat / 157
puncture hyperthermia depends on whether or not the Regio subthalamica is stimulated. But this does not exclude the corpus striatum from also exerting a certain effect on heat regulation. Rather, it is probable that impulses necessary for heat regulation proceed from the Corpus striatum to the Tuber cinereum. It is particularly interesting that the thermogenetic zone produces the temperature variation which Barbour and Hashimoto found on thermal stimulation of the Corpus striatum also through its direct cooling or warming, independent of the blood flow. Cooling of this zone results in a rise in temperature, and its warming results in a reduction in temperature. My experiments, which showed, on one hand, that the temperature rise from cold stimulation could be eliminated completely by preinjection with ergotoxin and, on the other hand, that the temperature drop due to warm stimulation could be prevented by atropine injection, allow me to accept Meyer's

hypothesis as best: that the thermoregulatory equipment of the homeothermic animals consists of sympathetic, thermogenetic heat centers and of parasympathetic, thermolytic cooling centers. We do not know whether the two are morphologically separable, but functionally it is probable, in so far as they behave antagonistically and balance each other. With respect to the localization of the sweat-generating zone, I was able to circumscribe a definite region.

This region extends from the caudal part of the Corpus mammillare to the basal cortical field of the frontal lobe, which is some 4 mm frontal from the Chiasma and 4 mm lateral from the midline. One can initiate profuse sweating from this sweat-generating zone through caloric as well as galvanic stimulation, while mechanical stimulation could not produce sweat secretion from any place on it. Of the sweat secretion produced by caloric stimulation, I could distinguish two types.

With respect to the character of the sweat secretion, I could also establish that the amount of sweat is very small with cold stimulation. With heat stimulation, in contrast, it is very abundant and profuse. Now, increased blood temperature has long been considered the only adequate physiological stimulus for the sweat centers. On the basis of my experiments, however, cold stimulus is also an adequate stimulus. These experimental results are also supported by the well-known fact that external cold does not have an absolute sweat-inhibiting effect. Even in healthy persons, but particularly in neurotics, secretion of a small amount of thick, viscous sweat, the /158 so-called cold sweat, can be observed, with a pale face, in the most severe winter cold. My experimental results further show that the small amount of sweating produced in the cat is not suppressed by atropine, but is completely prevented by ergotoxin; and, conversely, that the profuse sweating due to warming is inhibited not by ergotoxin, but by atropine. This indicates that with cold sweat we have sympathetic stimulation, while with heat sweat we have parasympathetic stimulation. It is probable, then, that along with the already demonstrated sympathetic pathway, there is still a parasympathetic sweat pathway. Although the sweat glands, as far as we know now, are only sympathetically innervated, their end apparatuses are affected by those poisons which otherwise attack parasynpathetic nerve endings. Even the specific sympathetic nerve poison, adrenalin, according to the latest study by Dieden [16], produces sweat on the cat foot pad under suitable experimental conditions. As sweat secretion, like saliva secretion, is stimulated both by sympathetic as well as by parasympathetic ending poisons, it is not improbable that the sweat glands, for which only sympathetic fibers have yet been demonstrated anatomically, are doubly innervated like the other autonomous organs, especially the salivary glands. Of the salivary glands, we know that they excrete abundant thin saliva on stimulation of the parasympathetic Chorda tympani and on injection of the parasympathetically active pilocarpine. On the other hand, they produce a small amount of viscous saliva on stimulation of the sympathetic system of the neck. On the basis of my observation, as well as clinical experience, one can also distinguish two different types of sweat secretion. The abundant, thin sweat is almost always linked with dilation of the skin vessels and reduction of temperature. Apparently it, like vasodilation, is due to a parasympathetic stimulus. The fact that it can be initiated by heat stimulation argues for that. The sparse, sticky, viscous sweat which appears linked with paleness of the face (anxiety, death sweat) could, like vasoconstriction, have its origin in sympathetic stimulation. Its initiation by a cold stimulus argues for that. In spite of detailed observation of the sweat centers in the Regio subthalamica, the effect of the cerebrum on sweat secretion has been neglected. We know from

experience that sweating is influenced by cerebral function. But the question of whether a second center for sweat secretion should be sought in the cerebral cortex is still unanswered and largely unattacked. Winkler localized the sweat-generating / 159
zone in the base of the frontal lobe. Recently, Pari [15] has likewise reported that the site of cerebral stimulation is in the basal and medial parts of the frontal lobe.

My experimental results could establish a close relation of the basal cortical field of the frontal lobe to sweating. This fact indicates that the superior sweat centers are in the basal and medial parts of the frontal lobe, in a close relation to the subordinate centers in the Regio subthalamica. In my experiments I have attempted to establish whether the sweating predominates on one or the other foot pad with unilateral stimulation of the sweat centers. I could establish no quantitative difference between the amounts of sweat on the two foot pads. This fact leads to the assumption that a partial crossing of the sweat pathways occurs. Finally, I could show an intimate relation of the shift in hydrogen ion concentration in the sweat centers to sweat secretion, observing that the direct application of acidified Ringer solution produces profuse sweating in the sweat-generating zone (see Figure 1).

Summary / 160

1. I was able to circumscribe a region in the Regio subthalamica of the cat which acts thermogenetically on both mechanical and electrical stimulation. This region extends from the caudal margin of the Corpus mammillare to the part directly frontal to the infundibulum, and extends some 4 mm laterally from the midline. At the level of the Tuber cinereum and of the Corpus mammillare, stimulation in the part which is no less than 1 mm and no more than 3 mm laterally from the midline

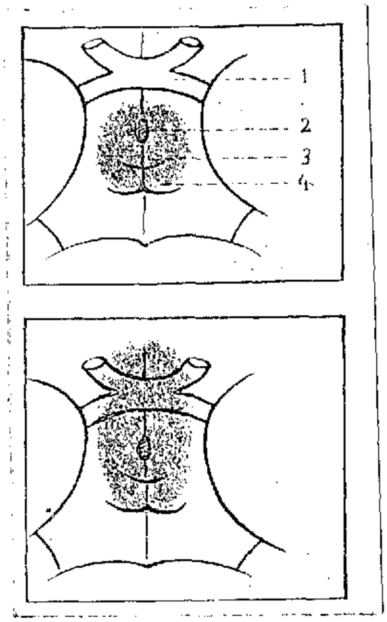

Figure 1. Regio subthalamica of the cat (for the anatomic relation of the various parts). 1 = Chiasma opticum. 2 = infundibulum. 3 = Tuber cinereum. 4 = Corpus mammillare. The shading in the upper figure indicates the thermoregulatory zone. The shading in the lower figure shows the sweat-producing zone.

gives the most significant effect. The farther the stimulation is from this region, medially or laterally, the less is its effect. At the level of the infundibulum, however, the points closest to it react with the greatest temperature rise. With the same conditions, those thermogenetic zones also reacted with a temperature rise to cold stimulus and with temperature lowering to heat stimulus.

2.) I also succeeded in establishing a remarkable relation between a definite place on the Regio subthalamica and of the basal cerebral cortex of the frontal lobe to sweating. This sweat-producing zone extends from the caudal end of the Corpus mammillare to the part which is some 4 mm frontal from the Chiasma and 4 mm lateral from the midline.

As for the intensity of sweat secretion on stimulation of the various parts of the zone, I have observed the same behavior as on stimulation of the heat centers.

3. Heat stimulation of this zone caused profuse sweating. Cold stimulation produced only a little secretion of sweat. The sweat secretion from heat stimulus is not affected by ergotoxin but is suppressed by atropine, while the sweat secretion from cold stimulus is not affected by atropine, but is suppressed by ergotoxin. Accordingly, one can distinguish two types of sweat secretion: our experimental results make it probable that the sweat-producing impulses produced by cold are carried by the sympathetic nervous system, while those due to heat are carried by the parasympathetic system to the active organs.

4. Unilateral stimulation of the sweat centers produces sweating on the foot pads not only on the same side but also on the opposite side. This suggests that a partial crossing of the sweat pathways occurs.

5. Shift of the hydrogen ion concentration in the sweat centers toward the acid side results in strong stimulation of /161
the centers, while a shift to the alkaline side has no effect on the sweat centers.

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